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A Multicentric Observational Study on Azilsartan to Assess the Efficacy, Safety and Tolerability in the Management of Hypertension in Indian Population: ZEAL Study

Uday M Jadhav [a++], B C Kalmath [b#], Manjula S [c*] and Krishna Kumar M [c]

[a] MGM New Bombay Hospital, Mumbai, Maharashtra, India.
[b] Bombay Hospital Institute of Medical Science, Mumbai, Maharashtra, India.
[c] Department of Medical Services, Micro Labs Limited, Bangalore, Karnataka, India.

Authors' contributions

This work was carried out in collaboration among all authors. All the four authors contributed equally in managing literature search, designing and conduct of the study, performed the statistical analysis, wrote the protocol, and the first draft of the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Background: Azilsartan is a recently approved angiotensin receptor blocker (ARB) available for the treatment of hypertension in India. Azilsartan has demonstrated unique properties which are different from the previous ARBs. The study objective was to assess the efficacy, safety of azilsartan in Indian subjects with hypertension.

[++] Consultant Cardiologist;
[#] Interventional Cardiologist;
**Corresponding author: Email: drmanjulas@gmail.com;*

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Methodology: The ZEAL study (AZilsartan Efficacy, SAfety and ToLerability Study) was an open label, non-comparative, multi-centric, observational study in Indian adult hypertensive patients. 152 centres were included in this study from across India by convenience sampling. Informed consent was taken from all participating subjects. Azilsartan 80 mg once daily was administered for 12 weeks. The primary outcome measure was decrease in mean seated systolic blood pressure (SBP) and diastolic blood pressure (DBP) at the end of 12 weeks from the baseline value. The secondary outcome measure included Global assessment of efficacy as evaluated by physician using a 4-point scale.

Results: A total of 4560 subjects were recruited in the study, 30 subjects each from 152 centres. 4416 subjects completed the 12-weeks study. Among them 2881 (65.3 %) were men and 1535 (34.7%) women. Mean age of the subjects during the recruitment was 53.6 ± 10.79 years. In our study, at the baseline, the mean SBP and mean DBP was 152.33 ± 16.39 mm Hg and 94.06±8.74 mm Hg respectively. At 6 weeks, the mean SBP was 143.9±13.6 mm Hg (∆8.43 ± 4.1 mm Hg) and 133.7±9.2 mm Hg (∆18.63±7.2 mm Hg) at the end of 12-weeks study which was clinically and statistically significant (P<0.05). Azilsartan was well tolerated. Global assessment of efficacy as evaluated by physician using a 4-point scale was very good or excellent for 77.8% of the study subjects.

Conclusion: Azilsartan effectively reduced SBP and DBP in the study subjects and was well tolerated. Azilsartan is a valuable option for achieving BP targets.

Keywords: Hypertension; azilsartan; angiotensin receptor blocker; blood pressure;

1. INTRODUCTION

"Hypertension is a leading cause of preventable death in developed nations and of increasing prevalence in developing countries" [1]. "Hypertension is a powerful risk factor for excessive morbidity and mortality globally including in India" [2]. "The burden of Hypertension is ever increasing in the last two decades" [2,3]. "Despite the availability of antihypertensive agents with various mechanisms of actions, only 13.8–32.5% of patients globally have adequately controlled hypertension. Nearly one-fifth of the global burden of 212 million disability-adjusted life year (DALYs) related to blood pressure is from India" [4].

"Clinical studies have shown that antihypertensive therapy reduces the risk of cardiovascular morbidity and mortality. Every 10 mmHg reduction in BP is associated with a reduction in stroke by 41%, coronary heart disease by 22%, and cardio-metabolic mortality by 41% to 46%" [5]. "The WHO report stresses on the importance of early detection and effective management in minimizing the risk of heart attacks, heart failure, stroke, and kidney failure. Early detection and effective management of hypertension remain the cornerstone of primary prevention of cardiovascular disease (CVD)" [5].

An overactive renin-angiotensin-aldosterone system (RAAS) is strongly linked to hypertension, as it regulates the hemodynamic equilibrium, circulating volume, and electrolyte balance. Therefore, RAAS inhibition forms the cornerstone for antihypertensive therapy [6]. Studies have shown that RAAS inhibition results in the reduction of proteinuria, thereby slowing the progression of chronic kidney disease (CKD) [7].

"Angiotensin II receptor blockers (ARBs) have selective angiotensin (AT) 1 receptor antagonism, and thereby reduce vasoconstriction, sympathetic stimulation, oxidative stress, release of inflammatory factors, and aldosterone release. ARBs lack angiotensin II escape, which is seen in ACEIs. A systematic review of 61 clinical trials comparing ACEIs and ARBs showed that the side effects of ACEIs, such as persistent cough, limited their use, whereas ARBs were better tolerated and assured continuity of treatment" [8].

"In 1995, Losartan was approved in the United States; this was followed by the approval of 6 more ARBs, valsartan, candesartan, irbesartan, telmisartan, olmesartan and azilsartan. In an effort to find a new class of AT1 agonists to achieve better control of BP than that provided by other ARBs and to provide significant clinical value beyond that afforded by good BP control, the newer ARB azilsartan was discovered by

modifying the tetrazole ring present in candesartan" [9].

"Azilsartan selectively blocks the binding of angiotensin II to the angiotensin II receptor, type 1 (called the AT1 receptor) found in the vascular smooth muscle and adrenal gland. Thus, as an angiotensin receptor blocker, azilsartan promotes vasodilation and a decrease in the effects of aldosterone. Compared with the other ARBs, azilsartan is a highly selective antagonist for the AT1 receptor – that is, it exhibits a greater affinity for the AT1 receptor compared with the AT2 receptor (angiotensin receptor-type 2) and produces better anti-hypertensive action" [9,10].

Azilsartan is the latest ARB available in India for the management of hypertension and there is paucity of data in the Indian population. The purpose of the study is to assess the efficacy, safety of azilsartan in Indian subjects with hypertension.

2. MATERIALS AND METHODS

The ZEAL study (AZilsartan Efficacy, SAfety and ToLerability Study) was an open label, non-comparative, multi-centric, observational study conducted between July 2017 and June 2018 in Indian adult hypertensive patients with azilsartan 80 mg treatment once daily for 12 weeks.

About 152 centres were included in this study from across India by convenience sampling. Informed consent was taken from all participating subjects. Every tenth consecutive patient were considered for the study from each centre as per the study inclusion and exclusion criteria.

The inclusion criteria were all male and non-pregnant female subjects above 18 years. The subjects with sitting systolic blood pressure of ≥130 mmHg and <180 mmHg or sitting diastolic blood pressure of ≥80 mmHg and <110 mmHg at the start of the treatment period, no change in diet/exercise therapy during the 3 months before the informed consent in a subject who has been on diet/exercise therapy and instructed to improve life style (e.g., diet and exercise) were included. Sitting blood pressure was measured until 3 consecutive stable measurements are obtained and the average value of the last 3 measurements was recorded.

The exclusion criteria included pregnant or breast feeding women, subjects with serious disorders which may limit the ability to evaluate efficacy or safety of the investigational products, including cerebrovascular, cardiovascular, renal, respiratory, hepatic, gastrointestinal, endocrine or metabolic, haematologic or neurologic and psychiatric diseases, history of angioedema related to ACE inhibitors or angiotensin II receptor blockers, non-compliant with the study medication or any study related procedures, patients with contraindications or hypersensitivity to Azilsartan, any other clinical condition which, in the opinion of the investigator, would not allow safe completion of the protocol and safe administration of the trial medication and subjects participating in another investigational drug within 4 weeks of enrolment into study.

The primary outcome measure was decrease in mean seated SBP and DBP at the end of 12 weeks from the baseline value. The secondary outcome measure included Global assessment of efficacy as evaluated by physician using a 4-point scale. Physical and systemic examination data and BP measurements of each recruited subject was done before initiating therapy (baseline) and at the end of 3 months (post treatment).

Demographic characteristics and results are summarized with descriptive statistics, including mean and standard deviation (SD) for continuous variables, and frequency and percentages for categorical variables. Student t-test is used and $P \leq 0.05$ is considered to be significant.

3. RESULTS

A total of 4560 subjects were recruited in the study, 30 subjects each from 152 centers. 4416 subjects completed the 12-weeks study. Among them 2881 (65.3%) were men and 1535 (34.7%) women. Mean age of the subjects during the recruitment was 53.6 ± 10.79 years. Mean weight was 71.78 ± 9.08 kg, and mean BMI was 27.69 ± 4.28 kg/m^2 (Table 1).

Table 1. Demographic characteristics of the participants

Mean Age (in years)	53.6 ± 10.79
Gender Men, N (%)	2881 (65.3 %)
Women, N (%)	1535 (34.7%)
Mean Height (in cm)	161 ± 14
Mean Weight (in kg)	71.78 ± 9.08
Mean BMI (in kg/m^2)	27.69 ± 4.28
Smoking, N (%)	930 (21.05%)
Alcohol, N (%)	1286 (29.12%)
Naïve to Treatment, N (%)	494 (11.18%)
Family history of Heart diseases, N (%)	785 (17.7%)
Co-morbidities, N (%)	3,076 (69.6%)

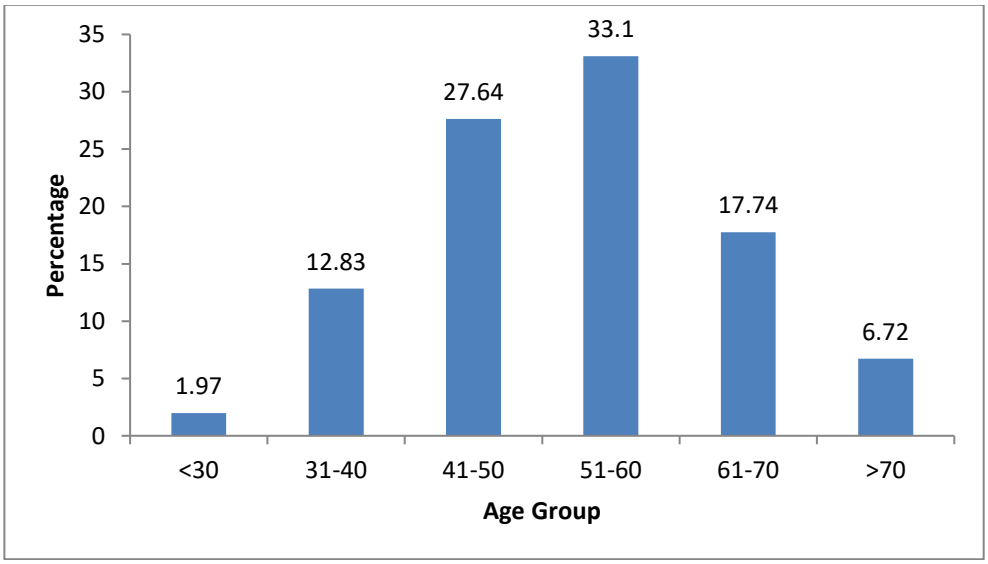

Fig. 1. Age group distribution of study participants

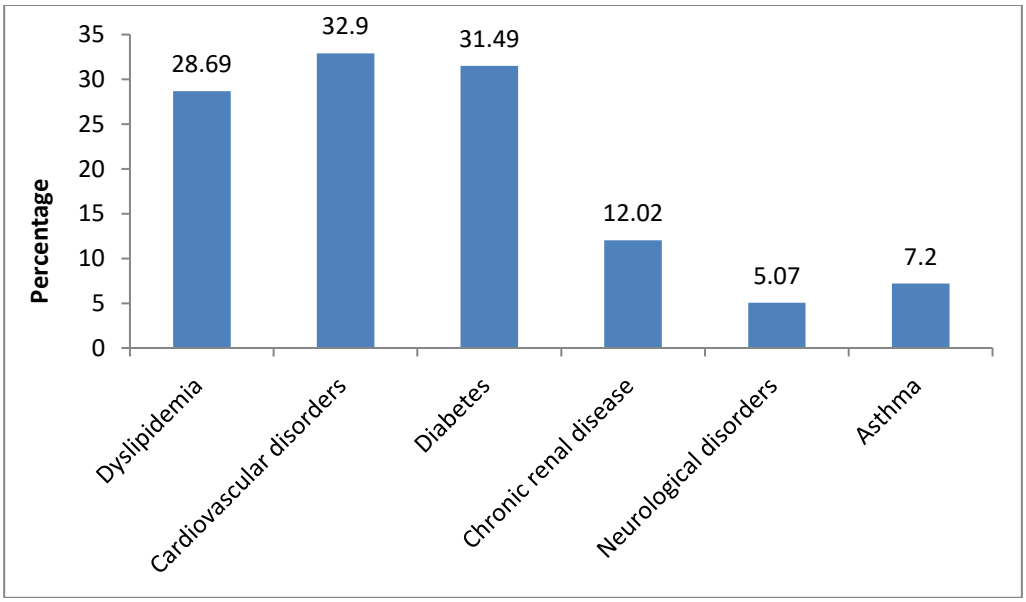

Fig. 2. Distribution of co-morbidities among study participants

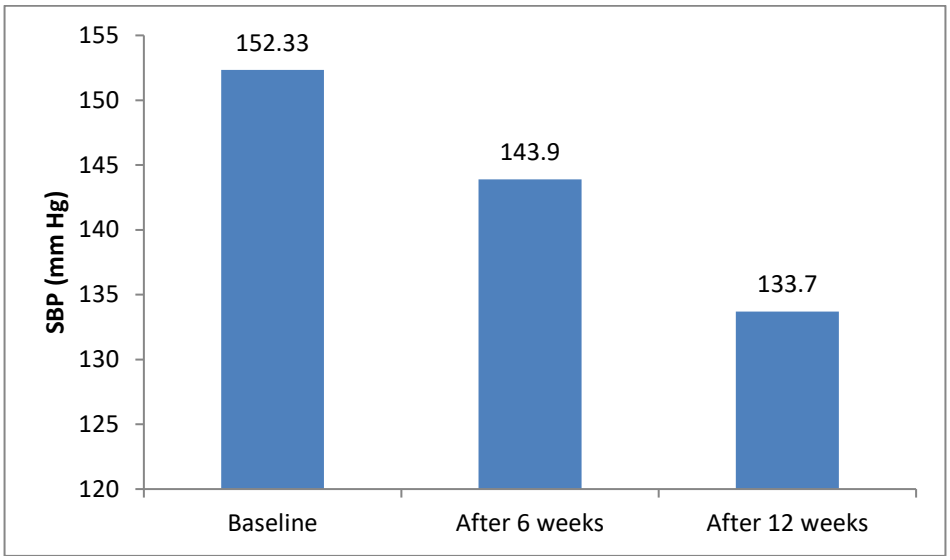

Fig. 3. Changes in the systolic blood pressure among study participants

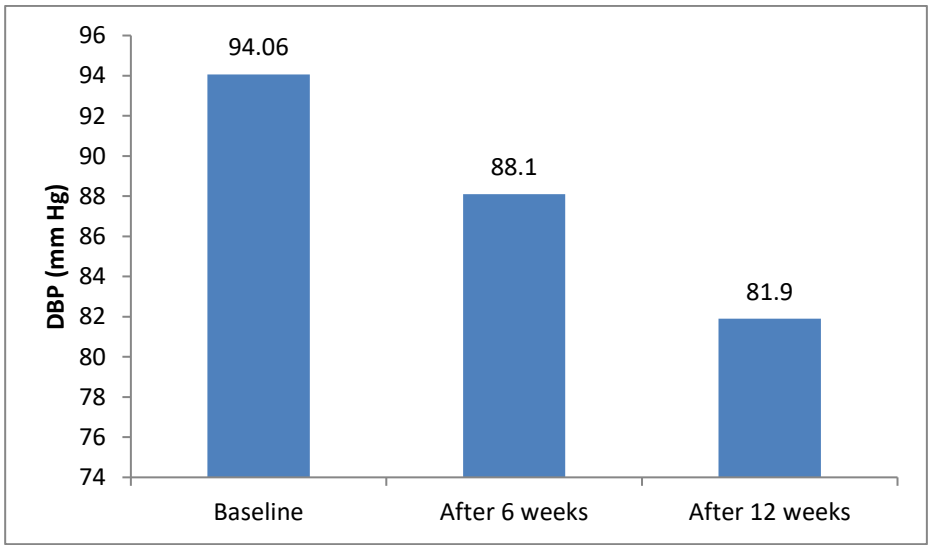

Fig. 4. Changes in the Diastolic Blood Pressure among study participants

The participant patient age group distribution is represented in detail in Fig. 1. of the included population, 21.05% were smokers whereas 29.12% were chronic alcoholics. In the study, 11.18% of the study subjects were Naïve to Treatment and Family history of CHD was seen in 17.7% of the study subjects.

About 69.6% of the study subjects had co- morbidities. Cardiovascular disorders, dyslipidemia, diabetes were the common comorbidities. The other co-morbidities were chronic renal disorders, neurological disorders and asthma (Fig. 2).

3.1 Mean Change in SBP and DBP after Treatment for 12 Weeks

There was a significant reduction of systolic and diastolic blood pressure after 12 weeks of treatment with Azilsartan in the study subjects. At the baseline, the mean SBP was 152.33 ± 16.39 mm Hg. At 6 weeks, the mean SBP was 143.9 ± 13.6 mm Hg (∆8.43 ± 4.1 mm Hg) and 133.7 ± 9.2 mm Hg (∆18.63 ± 7.2 mm Hg) at the end of 12-weeks study (Fig. 3).

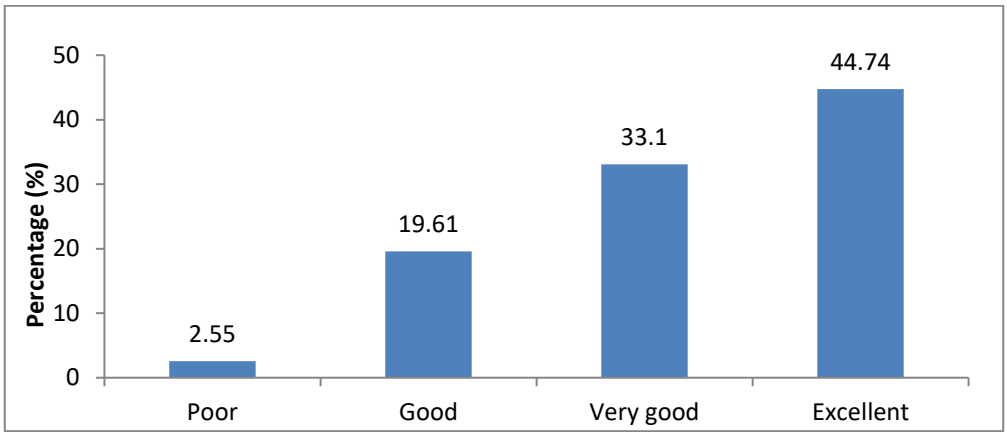

Fig. 5. Investigators grading for patients on study medication

The mean DBP at baseline was 94.06 ± 8.74 mm Hg. The DBP reduced to 88.1 ± 10.9 mm Hg (∆5.96 ± 2.3 mm Hg) from baseline at 6 weeks. The DBP was further reduced to 81.9 ± 8.8 mm Hg (∆12.16 ± 4.7 mm Hg) from baseline at the end of the study (Fig. 4).

In our study, overall, the adverse events reported were generally mild. The total number of AEs reported was less than 2.74% of total study population. Adverse events (AEs) reported by subjects included Increase in blood creatinine (0.06%), dizziness (0.92%), fatigue (0.36%), headache (0.58%), blood uric acid increased (0.15%), nausea (0.52%), diarrhoea (0.11%) and these were mostly transient and mild. Physician global severity assessments were also made at the end of the study visit on a four-point scale poor, good, very good, excellent. The global assessment of efficacy as evaluated by physician using a 4-point scale was very good and excellent for 77.8% of the study subjects (Fig. 5).

4. DISCUSSION

Hypertension is a leading cause of preventable death in developed nations and of increasing prevalence in developing countries. Uncontrolled hypertension greatly increases the risk of cardiovascular disease, cerebrovascular disease, and renal failure.

Azilsartan is a recently approved ARB available in the clinical arena for the treatment of hypertension. It has a distinctive “oxadiazolone” ring not found in any other ARB; this ring provides azilsartan a superior BP-lowering potency than other ARBs. It is a selective and competitive antagonist that blocks angiotensin II stimulation of AT1 receptors; it also acts as an inverse agonist and inhibits AT1 receptor signaling that may occur in the absence of angiotensin II. Azilsartan, the newest ARB has been shown to potentiate the functions of ang-(1-7) and block the functions of angiotensin-II. These combined actions of azilsartan make it an extraordinary molecule in the ARB class.

Azilsartan has 10,000-fold greater affinity for AT1 receptors versus AT2 receptors, shows superior BP lowering effect of Azilsartan. Azilsartan tightly binds with AT1 receptor for a longer period of time and dissociates more slowly than any other ARB. This contributes to its longer duration of action. These properties make azilsartan to provide more effective and sustained 24-hour BP control than other drugs in the same group. The peak plasma concentration of azilsartan achieved after oral administration of its 80 mg maximum approved dose is 5 times greater than the peak plasma concentration of olmesartan that is achieved after administration of its 40 mg maximum approved dose.

The study was conducted to assess the efficacy, safety of azilsartan medoxomil (AZM) in Indian subjects with hypertension. In our study, the mean age of the subjects was 53.6 ± 10.79 years. 60% of the study subjects were between 40-60 years. This was similar to the study published by Anchala et al. [11]. “Also, 21.05% of the study subjects were smokers and chronic alcoholism was documented in 29.12% of the study subjects. Smoking is one of the prime cardiovascular risk factors. Cessation of smoking and moderation of alcohol should be an important strategy to achieve BP goal as well as to reduce overall cardiovascular risk” [12,13].

“Studies have shown that Lowering of 24-hour BP in hypertensive patients is significantly more

than the maximum approved dose of olmesartan medoxomil and valsartan with Azilsartan" [14]. "In head-to-head studies using ABPM in hypertensive patients without serious comorbidities, treatment for 6 weeks with 80 mg azilsartan medoxomil lowered 24-hour SBP by 2 to 4 mm Hg more than 40 mg olmesartan medoxomil or 320 mg valsartan, respectively" [15]. "In a longer study comparing azilsartan medoxomil and valsartan, treatment with either 40 mg or 80 mg azilsartan medoxomil for 24 weeks reduced 24-hour SBP and clinic SBP significantly more than 320 mg valsartan" [14].

In our study, at the baseline, the mean SBP and mean DBP was 152.33 ± 16.39 mm Hg and 94.06±8.74 mm Hg respectively. At 6 weeks, the mean SBP was 143.9±13.6 mm Hg (∆8.43 ±4.1 mm Hg) and 133.7±9.2 mm Hg (∆18.63±7.2 mm Hg) at the end of 12-weeks study. Bakris et al. in their study with study subjects from 140 centers in the United States, Peru, Argentina, and Mexico reported that there was a reduction of SBP by 14.6 mm Hg after 6 weeks of treatment with Azilsartan [15]. The study by Weber et al. which included 566 patients with hypertension reported that the reduction of SBP with Azilsartan was 16.9 mm Hg at the end of the study [16]. In a phase 3, randomized, double-blind, placebo-controlled study, the mean reduction in SBP was 23.7 mmHg and DBP was 11.7 mmHg after 6 weeks of treatment with Azilsartan [17]. Even our study demonstrated the usefulness of Azilsartan. The incidence of other adverse events was low in our study which were mostly transient and mild. The results are consistent with the studies [14-16]. Azilsartan was well tolerated and there was no study discontinuation from any of the study subjects.

The present study holds significant relevance as there are limited studies evaluating the efficacy of azilsartan in the Indian population. One of the major strengths of the study is the robust enrolment of a diverse and clinically defined study population. Additionally, the study has gathered comprehensive baseline characteristics, including demographic information and co-morbid conditions. However, limitations include shorter study duration, conducted only in Indian population, absence of a placebo control, and limited diversity in reported adverse events. So, it was recommended to conduct the study in wider population of different races and with longer study period.

5. CONCLUSION

Azilsartan is the newer and the eighth ARB available in India. Studies have demonstrated that Azilsartan achieves a greater reduction in BP than other RAAS blockers. Our study highlights that Azilsartan is well tolerated and an effective option in the management of patients with hypertension in India. Thus, Azilsartan is a favourable addition to the therapeutic armamentarium of hypertension management.

CONSENT

As per international standards or university standards, patient(s) written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

The study was conducted after receiving approval from Ethics Committee and was registered with the Clinical Trial Registry of India (CTRI, reference number CTRI/2018/05/014285).

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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